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(54)【発明の名称】多孔質リン酸カルシウム系焼結体ブロックへの薬剤の含浸法

(57)【要約】

【課題】　効率よく薬剤を含浸させることができ、薬剤の長期徐放に好適な薬剤含有ブロックを大量生産しうる多孔質リン酸カルシウム系焼結体ブロックの含浸法を提供すること。

【解決手段】　連続気孔を有する多孔質リン酸カルシウム系焼結体ブロックに薬剤を含浸させるにあたり、そのブロックを薬剤溶液中に浸漬し、６３～２５４ｍｍＨｇの減圧度で５～２０分間含浸させることを特徴とする多孔質リン酸カルシウム系焼結体ブロックへの薬剤の含浸法である。

1

【特許請求の範囲】

【請求項１】　連続気孔を有する多孔質リン酸カルシウム系焼結体ブロックに薬剤を含浸させるにあたり、そのブロックを薬剤溶液中に浸漬し、６３～２５４ｍｍＨｇの減圧度で５～２０分間含浸させることを特徴とする多孔質リン酸カルシウム系焼結体ブロックへの薬剤の含浸法。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は、連続気孔を有する多孔質リン酸カルシウム系焼結体ブロックに抗癌剤、抗菌剤などの薬剤を含浸させる方法に関する。

【０００２】

【従来の技術】現在までに、多種類の抗菌剤が開発され、使用されているにもかかわらず、慢性骨髄炎は、依然として難治性疾患の一つとして挙げられる。慢性骨髄炎は、多くの場合、保存的治療のみで根治することは難しく、病巣掻爬を伴う外科的治療が必要となる。そのため従来より、持続的洗浄法、血管柄つき骨移植法、抗菌薬含有セメントビーズ法等の種々の治療法が開発されてきているが、いずれも一長一短があり、依然として治療に難渋することには変わりがない。また、骨及び軟部悪性腫瘍では抗癌剤の体内静注療法、持続動脈内注入療法、放射線療法などが行われている。しかし、これらは、正常細胞に悪影響を与え、持続動脈内注入療法も長期にわたるため、患者に与えるストレスは大きい。

【０００３】これまでに、本発明者は、骨髄炎の治療に従来から骨欠損部の充填材料として利用されてきた多孔質ハイドロキシアパタイトブロックの連続気孔内に抗生剤を遠心法により含浸させ、骨髄炎の一期的治療に基礎実験及び臨床使用で成功したことを報告した〔Ｊ．Ａｐｐｌ．Ｂｉｏｍａｔｅｒ．、６（３）：１６７～１６９（１９９５）、Ｊ．Ｏｒｔｈｏｐ．Ｓｕｒｇ．、２（２）：４７～５０（１９９４）及びＣａｎｃｅｒ Ｌｅｔｔｅｒｓ、１０７：１１～１８（１９９６）〕。しかしながら、この遠心法は、工業的な大量生産には困難が伴っていた。

【０００４】

【発明が解決しようとする課題】本発明は、前記の従来技術の問題点を解消し、多孔質リン酸カルシウム系焼結体ブロックに効率よく薬剤を含浸させることができ、薬剤の長期徐放に好適な薬剤含有ブロックを大量生産しうる方法を提供することを目的とする。

【０００５】

【課題を解決するための手段】本発明は、多孔質ブロックを薬剤溶液中に浸漬し、特定の減圧下に一定時間含浸させることによって上記目的を達成したものである。すなわち、本発明の多孔質リン酸カルシウム系焼結体ブロックへの薬剤の含浸法は、連続気孔を有する多孔質リン酸カルシウム系焼結体ブロックに薬剤を含浸させるにあたり、そのブロックを薬剤溶液中に浸漬し、６３～２５４ｍｍＨｇの減圧度で５～２０分間含浸させることを特徴とする。

2

【０００６】

【発明の実施の形態】本発明に用いるブロックは、骨補填材として知られている連続気孔を有する多孔質リン酸カルシウム系焼結体ブロックであれば、特に制限はなく、様々なものを使用することができる。リン酸カルシウムとしては、例えば、ハイドロキシアパタイト、フッ素アパタイト、リン酸水素カルシウム、リン酸三カルシウム、リン酸四カルシウムなどから選ばれた１種又は２種以上を使用することができる。これらのうちハイドロキシアパタイトを主成分とするものが最も好ましい。

【０００７】本発明に用いる多孔質ブロックの気孔率や気孔径には、特に制限はなく、ブロックの使用目的、適用箇所などに応じて適宜選択することができる。具体例としては、平均孔径０．０１～２０００μｍの連続気孔と平均孔径０．０１～３０μｍの独立気孔を有するリン酸カルシウム系焼結体（特開昭６３－１２５２５９号公報参照）、孔径２０～２０００μｍのマクロポアと粒子間隙からなる三次元連通孔とを有するリン酸カルシウム系焼結体（特開平２－１６７８６８号公報参照）などが挙げられ、気孔率は５～７５％であるのが好ましい。これらの多孔質焼結体ブロックは、生体適合性、機械的強度、切削性に優れ、インプラント手術に際して術前、術中におけるトリミング加工が容易であり、さらに気孔より体液流通がなされるため、カプセル反応を効果的に防止できるとともに、骨補填材として使用したときに骨形成の場を提供して新生骨との複合化を効果的に行うことができる点で好適である。

【０００８】多孔質リン酸カルシウム系焼結体ブロックは、様々な方法で製造することができ、例えば、リン酸カルシウム系原料スラリーに過酸化水素水や卵白アルブミン等の発泡剤を加え、発泡、乾燥後、９００～１４００℃で焼成する方法、連続気孔を有する熱分解性物質（ポリウレタンフォーム等）にリン酸カルシウム系原料スラリーを付着させ、９００～１４００℃で焼成する方法、リン酸カルシウム系原料粉末に加熱によって消失する物質粒子を加え、プレス等で成形し、９００～１４００℃で焼成する方法、リン酸カルシウム系原料粉末を転動造粒機等で造粒し、得られた造粒体をポリビニルアルコール等の有機バインダーで結合し、９００～１４００℃で焼成する方法、リン酸カルシウム系原料粉末と高分子物質と気泡とを含むスラリー又は流動性ゲルを注型し、増粘又はゲル化して気泡を保持させ、乾燥させ、９００～１４００℃で焼成する方法などによって製造することができる。

【０００９】本発明の方法では、まず、減圧を加えうる容器内に入れた薬剤溶液中に上記のようなブロックを入れ、薬剤溶液中に浸漬する。薬剤としては、抗菌剤、抗

生物質、抗癌剤など、様々な薬剤を用いることができ、薬剤溶液の濃度についても薬剤の種類や目的などに応じて適宜選定することができる。容器に入れる薬剤溶液の量は、ブロックを浸漬し、溶液を充分に含浸させた後も、ブロック全体が溶液中に水没している程度とする。

【００１０】ブロックを薬剤溶液に浸漬した後、本発明においては、容器内を６３～２５４ｍｍＨｇ、好ましくは１２０～２５４ｍｍＨｇの減圧度とし、５～２０分間ブロックに薬剤溶液を含浸させる。減圧度が６３ｍｍＨｇ未満であると、ブロック内への薬剤の含浸率が充分に向上せず、２５４ｍｍＨｇを超える減圧度にしてもそれ以上にはあまり薬剤の含浸率が増大せず、経済的でない。減圧度が１２０～２５４ｍｍＨｇであるとき、特に顕著な含浸率の向上が認められた。減圧度は、真空ポンプ、人工関節用セメントバキューム装置など、任意の装置を用いて調整することができる。含浸時間は、ブロックの大きさやブロックの気孔率、気孔径などを考慮して適宜決定することができるが、５分未満では充分な含浸が行われず、２０分を超えて含浸してもほとんど含浸率の向上は期待できない。

【００１１】薬剤溶液を含浸したブロックは、そのまま使用することもできるが、必要に応じて自然乾燥あるいは加熱乾燥することもできる。アミノグリコシド系の薬剤など、薬剤が熱に強い物質であれば、乾熱１６０℃の滅菌で乾燥を行うこともできる。

【００１２】

【実施例】次に、実施例に基づいて本発明を詳細に説明するが、本発明はこれによって制限されるものではない。

【００１３】実施例１

（１）多孔質ハイドロキシアパタイト焼結体ブロックの製造

１０００ｍｌのビーカーに水４５０ｇを入れ、メチルセルロース（和光純薬工業株式会社製、２％水溶液として２０℃で測定した粘度が４０００ｃｐｓのもの）８．１ｇを添加し、ハンドミキサーで３分間撹拌してメチルセルロースの水溶液を調製した。このビーカーを６０℃の恒温槽に入れ、ビーカー内のメチルセルロース水溶液を撹拌しながら４０℃まで昇温し、さらに３０秒間撹拌し、気泡を含む流動性ゲルとした。他方、公知の湿式合成法により製造したハイドロキシアパタイトスラリーを噴霧乾燥することにより平均粒径１２μｍに造粒し、さらにジェットミルで粉砕して平均粒径１０μｍの球状粉と平均粒径１μｍの微粉とからなるハイドロキシアパタイト粉体を調製した。上記ビーカーを恒温槽の外に取り出し、調製したハイドロキシアパタイト粉体１５０ｇを少量ずつ徐々に混合し、粘度を測定した後、２００ｍｌのガラスビーカーに流し入れた。このビーカーを９０℃の乾燥機に２４時間入れて内容物をゲル化し、乾燥させ、ハンドソーで２９．４×２９．４×２９．４ｍｍの立方体に切り出し、これを下記の焼成パターンで焼成した。室温から５０℃／時の昇温速度で６００℃まで昇温し、次に１００℃／時の昇温速度で１２００℃まで昇温し、この温度で４時間焼成した後、５０℃／時の降温速度で６００℃まで冷まし、この温度に４時間保持した後、１００℃／時の降温速度で室温まで冷ました。得られた焼結体の寸法は、２０×２０×２０ｍｍであり、気孔率は５０％であった。

【００１４】（２）薬剤含浸

上記（１）で得られた焼結体ブロックの体積（８ｃｍ³）の１５０％となる量で１重量％エオシン水溶液を入れた減圧可能な容器を１６個準備し、それぞれのエオシン水溶液中に焼結体ブロックを浸漬し、２５４ｍｍＨｇ、１２７ｍｍＨｇ、６３．５ｍｍＨｇ、０ｍｍＨｇの陰圧を加え、焼結体ブロックへのエオシン溶液の含浸率の経時変化を観察した。含浸率は、焼結体ブロックの含浸前後での重量の増加量により次式から求め、結果を図１に示す。

含浸率＝〔減圧後の増加量（ｇ）を（ｍｌ）に変換／８ｍｌ〕×１００

【００１５】図１から判るように、含浸開始から５分間は、いずれの場合も急激に含浸率が上昇したが、６３．５～２５４ｍｍＨｇの減圧度の場合には、減圧しなかった場合（減圧度０ｍｍＨｇ）に比べて含浸率が著しく向上しており、５分～１５分で徐々に含浸率が向上し、１５～２０分でほぼ平衡状態となった。焼結体ブロックの体積に対するエオシン溶液の最大含浸率は、減圧しなかった場合には約２３％であったが、減圧した場合で約４０％であった。また、上記の含浸したブロックを図２に示すように歯科用電動ドリルで割断し、赤色エオシンによる含浸領域を肉眼で観察したところ、減圧しなかった場合には、中心部にはエオシンは到達していなかったが、本発明により１２７～２５４ｍｍＨｇの減圧度で減圧した場合には中心部まで着色しており、エオシン溶液が到達していることが確認された。なお、上記実施例では、含浸状態を肉眼で観察できるように、薬剤溶液として色素溶液を用いたが、実際には、言うまでもなく抗菌剤、抗生物質、抗癌剤などの各種の医薬品の溶液を用いるものである。

【００１６】

【発明の効果】本発明の含浸法によれば、多孔質リン酸カルシウム系焼結体ブロックの気孔内に極めて簡単な操作で効率よく薬剤を含浸させることができ、しかも高い含浸率を短時間で達成できるため、薬剤の長期徐放に好適な薬剤含有ブロックを大量生産することができ、骨補填材として使用するのに好適な高い機械的強度を有し、生体適合性及び切削性に優れ、薬剤含有量の多い、薬剤徐放性ブロックを提供することができる。

【図面の簡単な説明】

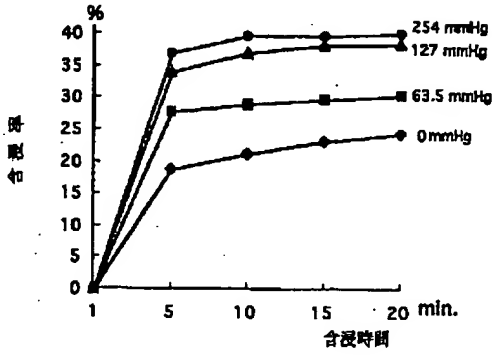
【図１】本発明の実施例で測定した各減圧度における薬

5　　6

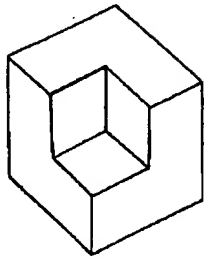
剤溶液の含浸率の経時変化を示すグラフ図である。　　のブロックの斜視図である。

【図２】実施例において含浸状態を観察するため割断後

【図１】



【図２】



Date: September 29, 2000

Declaration

I, Megumi Odawara, a translator of Fukuyama Sangyo Honyaku Center, Ltd., of 16-3, 2-chome, Nogami-cho, Fukuyama, Japan, do solemnly and sincerely declare that I understand well both the Japanese and English languages and that the attached document in English is a full and faithful translation, of the copy of Japanese Unexamined Patent No. Hei-10-279471 laid open on October 20, 1998.

M. Odawara

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Method of Impregnating Drug Into Porous Calcium Phosphate-based Sintered Block

Japanese Unexamined Patent No. Hei-10-279471

Laid-open on: October 20, 1998

Application No. Hei-9-88181

Filed on: April 7, 1997

Inventor: Bansei ITOKAZU

Applicant: Asahi Kogaku Kogyo Kabushiki Kaisha

SPECIFICATION

[TITLE OF THE INVENTION] Method of Impregnating Drug Into Porous Calcium Phosphate-based Sintered Block

[ABSTRACT]

[Theme] To provide a method of impregnating a porous calcium phosphate-based sintered block whereby a drug can be efficiently impregnated into the block, and mass production for drug-containing blocks which are suitable for long-term controlled release of the drug is possible.

[Solution Means] An impregnation method for impregnating a drug into a porous calcium phosphate-based sintered block having continuous pores, wherein the block is immersed in a drug solution, and the solution is impregnated for 5 to 20 minutes

at a pressure reduction by a degree of 63 to 254mmHg.

[WHAT IS CLAIMED IS;]

[Claim 1] A method impregnating drugs into a porous calcium phosphate-based sintered block for impregnating a drug into a porous calcium phosphate-based sintered block having continuous pores, wherein the block is immersed in a drug solution, and the drug is impregnated for 5 to 20 minutes at a pressure reduction by a degree of 63 to 254mmHg.

[DETAILED DESCRIPTION OF THE INVENTION]

[0001]

[Field of the Invention] The present invention relates to a method of impregnating a drug such as an anticancer drug or antibacterial agent into a porous calcium phosphate-based sintered block having continuous pores.

[0002]

[Prior Arts] Until now, although various kinds of antibacterial agents have been developed and used, chronic osteomyelitis is still an intractable disease. In many cases, complete cure of chronic osteomyelitis is difficult by conservative treatment only, so that surgical treatment accompanied by nidus curettage becomes necessary. Therefore, priorly, various treatment methods such as continuous deterging, transplantation of bone with blood vessels, and an antibacterial agent-containing

cement bead method has been developed, however, these methods have merits and demerits, so that the treatment of chronic osteomyelitis is still difficult. In addition, for treatment of bone and soft portion malignant tumors, internal body intravenous injection treatment and continuous intraarterial injection treatment of anticancer agents and radiotherapy have been performed. However, these treatment methods have harmful influences on normal cells, and continuous intraarterial injection treatment requires a long time period, so that patients are exposed to great stress.

[0003] The present inventor reported that an antibiotic agent was impregnated by a centrifugal method into a porous hydroxyapatite block which had been used as a filler for a portion of bone broken for treatment of osteomyelitis, which resulted in successful initial stage treatment of osteomyelitis in basic experiments and clinical use [J. Appl. Biomater., 6(3): 167-169 (1995), J. Orthop. Surg., 2(2): 47-50 (1994, and Cancer Letters, 107: 11-18 (1996)]. However, this centrifugal method is problematic in terms of industrial mass production.

[0004]

[Themes to be Solved by the Invention] The object of the invention is to provide a method whereby the problems in the

prior-art are solved, a drug can be efficiently impregnated into a porous calcium phosphate-based sintered block, and mass production of drug-containing blocks suitable for long-term controlled release of the drug is possible.

[0005]

[Means for Solving Themes] In the invention, a porous block is immersed in a drug solution, and at a predetermined degree of pressure reduction, the drug is impregnated for a predetermined period of time, whereby the abovementioned object is achieved. That is, the method impregnating drugs into a porous calcium phosphate-based sintered block of the invention is characterized in that, when a drug is impregnated into a porous calcium phosphate-based sintered block having continuous pores, the block is immersed in a drug solution, and the drug is impregnated for 5 to 20 minutes at a pressure reduction by a degree of 63 to 24mmHg.

[0006]

[Preferred Embodiment of the Invention] The block to be used in the invention is not especially limited as long as the block is a porous calcium phosphate-based sintered block having continuous pores which is generally known as a bone filler, so that various kinds of blocks can be used. As a calcium phosphate, one or more kinds selected among hydroxyapatite,

fluo-apatite, calcium hydrogenphosphate, tricalcium phosphate, and quatercalcium phosphate can be used. Among these, a substance containing hydroxyapatite as a main ingredient is most preferable.

[0007] The porosity and pore diameter of the porous block used in the invention are not especially limited, and they can be properly selected in accordance with the purpose of use and position of application of the block. As concrete examples, there are a calcium phosphate-based sintered body having continuous pores whose average pore diameter is 0.01 to 2000μm and independent pores whose average pore diameter is 0.01 to 30μm (refer to Japanese Unexamined Patent Publication No. Sho-63-125259), and a calcium phosphate-based sintered body having macro pores with diameters of 20 to 2000μm and 3-dimensional communication holes formed of particle spaces (refer to Japanese Unexamined Patent Publication No. hei-2-167868), and a porosity of 5 to 75% is preferable. These porous sintered blocks are excellent in biocompatibility, mechanical strength, and machinability, and when implant operation is conducted, trimming of them prior to or during the operation is easy, and furthermore, body fluid circulation is made through the pores, so that capsule reaction can be effectively prevented, and also, when the blocks are used as

bone fillers, they contribute to provide a space for bone formation and effective amalgamation with new bone. Therefore, these blocks are preferable.

[0008] The porous calcium phosphate-based sintered block can be produced by various methods, for example, a method whereby a foaming agent such as hydrogen peroxide water or albumen is added to a calcium phosphate-based raw slurry, and after foaming and drying, sintering is carried out at 900 to 1400℃, a method whereby substance particles which vanish when being heated are added to calcium phosphate-based raw powder, and the powder is molded by means of pressing and sintered at 900 to 1400℃, a method whereby calcium phosphate-based raw powder is formed into particles by a rolling granulator, and the obtained granular bodies are combined by a organic binder such as polyvinyl alcohol and sintered at 900 to 1400℃, and a method whereby a slurry or fluid gel containing calcium phosphate-based raw powder, a polymer, and bubbles is poured into a mold, is given increased viscosity, and gelated to hold bubbles, then dried, and sintered at 900 to 1400℃.

[0009] According to the method of the invention, first, the abovementioned block is put in and immersed in a drug solution in a container in which the pressure can be reduced. As a drug, various drugs such as an antibacterial agent, antibiotic agent,

and anticancer drug can be used, and the concentration of the drug solution can be properly selected depending on the kind of drug and its purpose. The amount of the drug solution to be put in the container is set to a degree so that the entirety of the block is still completely submerged in the solution after the block is immersed and the solution is sufficiently impregnated into the block.

[0010] After the block is immersed in the drug solution, in the invention, the pressure inside the container is reduced by 63 to 254mmHg, preferably, 120 to 254mmHg, and the drug solution is impregnated into the block for 5 to 20 minutes. If the degree of pressure reduction is less than 63mmHg, the impregnation rate of the drug into the block does not sufficiently increases, and even if the degree of pressure reduction is more than 254mmHg, the impregnation rate of the drug does not significantly increase, and this is not economical. When the degree of pressure reduction was 120 to 254mmHg, a significant improvement in the impregnation rate was shown. The degree of pressure reduction can be adjusted by optional devices such as a vacuum pump or artificial joint cement vacuum device. The impregnation time can be properly determined by considering the pore diameter, however, if the time is 5 minutes or less, impregnation is not sufficient, and

if impregnation is carried out for 20 minutes or more, improvement in the impregnation rate cannot be expected.

[0011] The block which is impregnated with the drug solution can be used as it is, however, it can be naturally dried or dried by heating before use. If the drug is a substance having great heat resistance such as an amino glycoside-base drug, drying can be applied while sterilizing at 160℃.

[0012]

[Example] Next, the invention shall be described in detail based on an example, however, the invention is not limited to this example.

[0013] Example 1

(1) Manufacture of Porous Hydroxyapatite Sintered Block

450g of water was poured into a 1000ml beaker, 8.1g of methylcellulose (produced by Wako Pure Chemicals Industries, Ltd., the measured viscosity of a 2% solution thereof is 4000cps) was added to the water, stirred for 3 minutes with a hand mixer, whereby a solution of methylcellulose was prepared. This beaker was put into a tank with a constant temperature of 60℃, heated to 40℃ while stirring the methylcellulose solution inside the beaker, and then further stirred for 30 seconds, whereby fluid gel containing bubbles was obtained. On the other hand, a hydroxyapatite slurry

prepared by means of the generally known wet synthesis method was sprayed, dried, and granulated so as to have an average particle diameter of 12μm, and further crushed by a jet mill, whereby hydroxyapatite powder consisting of spherical powder with an average particle diameter of 10μm and micro powder with an average particle diameter of 1μm was prepared. The beaker was removed from the constant temperature tank, the prepared 150g of hydroxyapatite powder was mixed into the beaker little by little, and then poured into a 200ml glass beaker after the viscosity was measured. This beaker was put into a drier at 90℃ for 24 hours to gelate the contents, the gelated contents was dried and cut into 29.4x29.4x29.4mm cubes, and the cubes were sintered by a sintering pattern as follows. The temperature was raised to 600℃ at a temperature raising rate of 50℃/h from the room temperature, next, raised to 1200℃ at a temperature raising rate of 100℃/h, and at this temperature, the cubes were sintered for 4 hours and then cooled to 600℃ at a temperature lowering rate of 50℃/h, and maintained for 4 hours at this temperature, and thereafter, cooled to the room temperature at a temperature lowering rate of 100℃/h. The dimensions of the obtained sintered bodies were 20x20x20mm, and the porosity was 50%.

[0014] (2) Drug Impregnation

16 containers in which the pressure can be reduced were prepared by filling them with a volume of eosin solution of 1 weight % that was 150% that of the sintered block ($8cm^2$) obtained by the abovementioned (1), the sintered blocks were immersed in each eosin solution, negative pressures of 254mmHg, 127mmHg, 63.5mmHg, and 0mmHg were applied, and changes with the elapse of time in the impregnation rate of the eosin solution into the sintered block were observed. The impregnation rate is calculated by the following formula from the amount of increase in weight of the sintered block after impregnation from the amount before impregnation, and the results are shown in Fig. 1.

Impregnation rate = [amount of increase after pressure reduction (g) is converted into (ml) / 8ml] x 100

[0015] As can be clearly understood from Fig. 1, within 5 minutes after the start of impregnation, the impregnation rate suddenly increased in all cases, however, in the case of the pressure reduction by a degree of 63.5 to 254mmHg, the impregnation rate significantly increased in comparison with the case where the pressure was not reduced (the degree of pressure reduction: 0mmHg), and the impregnation rate gradually increases after 5 minutes and within 15 minutes, and the rate turned into an equilibrium state after 15 minutes and

within 20 minutes. The maximum impregnation rate of the eosin solution into the volume of the sintered block was approximately 23% in the case where the pressure was not reduced, however, it was approximately 40% in the case where the pressure was reduced. In addition, When the abovementioned impregnated block was cut and divided by a dental electric drill as shown in Fig. 2 and the area impregnated with red eosin was observed by the naked eye, the eosin did not reach the center part in the case where the pressure was not reduced, however in the invention, it reached the center part in the case where the pressure was reduced by a pressure reduction by a degree of 127 to 254mmHg. That is, it was confirmed that the eosin reached to the center. Furthermore, in the abovementioned example, as the impregnation condition can be observed by the naked eyes, a colored solution was used as a drug solution, however, needless to say, solutions of various kinds of medicines such as an antibacterial agent, antibiotic agent, and anticancer drug are used in actuality.

[0016]

[Effects of the Invention] According to the impregnation method of the invention, a drug can be efficiently impregnated into pores of a porous calcium phosphate-based sintered block through extremely easy operations, and furthermore, a high

impregnation rate can be achieved in a short time, so that mass production of drug-containing blocks suitable for long-term controlled release of the drug is possible, and a drug releasing block which has high mechanical strength suitable for use as a bone filler, is excellent in biocompatibility and machinability, and contains a large amount of drug.

[BRIEF DESCRIPTION OF THE DRAWINGS]

[Fig. 1] A graph showing changes with elapse of time in the impregnation rate of a drug solution at each degree of pressure reduction measured in the example of the invention.

[Fig. 2] A perspective view of the block after being cut and divided for observation of the impregnation condition in the example.

Fig.1

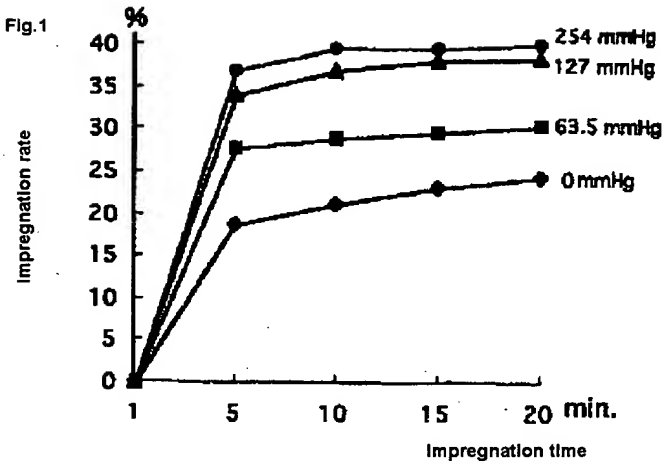
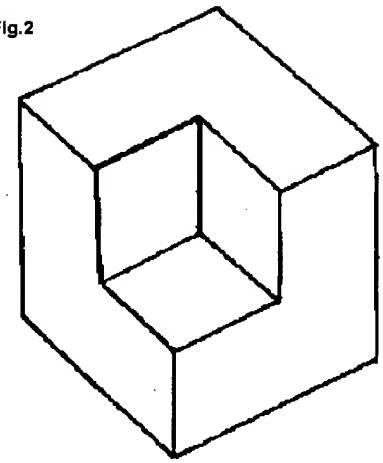

%
40
35
30
25
20
15
10
5
0
Impregnation rate
254 mmHg
127 mmHg
63.5 mmHg
0 mmHg
1
5
10
15
20 min.
Impregnation time

Fig.2



ヘテロポーラスハイドロキシアパタイトブロックからの薬物放出制御

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1．緒言

生体硬組織である骨は，無機物ハイドロキシアパタイト(HAP)が密に積み重なっている皮質骨と空隙の多い海面骨が形成されている．これらの空隙の分布により，軽量で強い構造を作り，また，適当な大きさの空隙の分布により細胞生理的な環境を整えている．人工骨として気孔率の高いアパタイトブロックは，細胞親和性が高く，人工骨としての生体適合性が高いことが知られている．しかし，その機械的強度は，極めて弱い．演者らは，生体骨の構造を模倣し新規の生体親和性機能を有する人工骨を得るために，アパタイトブロック中の空隙の幾何学的分布を制御して，ヘテロポーラスタイプのブロックを得た．これを薬物送達システム（DDS）の基材として適用し，薬物送達能を有する新規の人工骨の開発を検討した．

2．実験

気孔率の異なる30%，40%，50%の直径5mmφ，厚み2mmのHAPブロック（アパセラム，旭光学製）と外層と内層で異なる空隙を有する（外層/内層，30/50%，40/50%，50/50%）HAPブロックを調製した．HAPブロックの結晶性は，粉末X線回折，FTIRスペクトル，DTA分析により確認し，ブロックの空隙は，水銀ポロシメータにより測定した．HAPブロックに抗炎症剤インドメタシンエタノール溶液を含浸させドライヤーで乾燥し，一定量の薬物を含有させた．このブロックの骨への埋め込み時を想定し，外層面を残しシリコンゴムで固定した試料を調製し，擬似体液(SBF)中，37℃で薬物放出試験を行った．溶出薬物濃度は，UVスペクトルにより検量線を作成し分析した．

3．結果と考察

外層と内層で異なる空隙を有する（外層/内層，30/50%，40/50%，50/50%）HAPブロックの結晶性は，粉末X線回折，FTIRスペクトル，DTA分析により純粋なHAPであることを確認した．人工骨からの薬物放出速度はインプラントの外層の空隙が減少により低下し，外層の空隙が薬物の放出を制御していることが確認された．このことから，空隙分布を制御することにより，機械的強度が高く細胞親和性の高いHAPブロックは，その幾何学的構造から薬物の放出速度をも制御できる可能性が示された．

Contolled drug relase from hetero porous hydroxyapatite blouk

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Controlled Drug Release from Hetero Porous Hydroxyapatite Block

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1. Preface

Bone which is a living hard tissue consists of cortical bone formed of densely accumulated inorganic hydroxyapatite (HAP) and spongy bone having many pores. Due to the distribution of these pores, a strong structure with a light weight is formed, and due to the distribution of the properly sized pores, a physiological cell environment is achieved. It is generally known that an apatite block with high porosity used as artificial bone is high in cell affinity and biocompatibility. However, its mechanical strength is extremely weak. The researchers controlled the geometric distribution of pores inside an apatite block and obtained a hetero porous type block by imitating the structure of living bone in order to realize artificial bone which has a new function to achieve biocompatibility. They applied this block to use as a base material for a drug delivery system (DDS), and examined

development of new artificial bone having a drug delivery ability.

2. Experiment

HAP blocks (APACERAM produced by Asahi Optical Co., Ltd.), which were different in porosity from each other, that is, 30%, 40%, and 50%, and had a diameter of 5mm and a thickness of 2mm, and HAP blocks, each of which was different in porosity between its outer layer and inner layer (outer layer/inner layer: 30/50%, 40/50%, 50/50%), were prepared. The crystallinity of the HAP blocks was confirmed by means of powder X-ray diffraction, FTIR spectrum, and DTA analysis, and the pores in the blocks were measured with a mercury pore meter. The HAP blocks were impregnated with an indomethacin ethanol solution which is an antiinflammatory agent, dried with a dryer, and made to contain a predetermined amount of a drug. On the assumption that the blocks were implanted in bone, a sample fixed by silicon rubber while leaving the outer layer surface exposed was prepared, and then a drug release test was conducted at 37℃ in a pseudo-body fluid (SBF). The concentration of the eluted drug was analyzed from lines measured by means of UV spectrum.

3. Results and Examination

The crystallinity of the HAP blocks each of which was different in porosity between its outer layer and inner layer (outer layer/inner layer: 30/50%, 40/50%, 50/50%) is confirmed as pure HAP by means of powder X-ray diffraction, FTIR spectrum, and DTA analysis. It was confirmed that the speed of drug release from artificial bone lowered due to reduction in pores in the outer layer of the implant, and the pores in the outer layer controlled the drug release. From this fact, there is a possibility that, in HAP blocks having high mechanical strength and high cell affinity, the speed of drug release from its geometric structure can be controlled by controlling the distribution of pores.